

Effect of fluvoxamine on plasma risperidone concentrations in patients with schizophrenia

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Abstract

The effect of fluvoxamine on plasma concentrations of risperidone and its active metabolite 9-hydroxyrisperidone (9-OH-risperidone) was investigated in 11 schizophrenic patients with prevalently negative or depressive symptoms. Additional fluvoxamine, at the dose of 100 mg/day, was administered for 4 weeks to patients stabilized on risperidone (3–6 mg/day). Mean plasma concentrations of risperidone, 9-OH-risperidone and the active moiety (sum of the concentrations of risperidone and 9-OH-risperidone) were not significantly modified following co-administration with fluvoxamine. After 4 weeks, fluvoxamine dosage was increased to 200 mg/day in five patients and then maintained until the end of week 8. At final evaluation, mean plasma levels of risperidone active moiety were not modified in the six patients who were still receiving the initial fluvoxamine dose, while concentrations increased slightly but significantly (by a mean 26% over pretreatment; $P < 0.05$) in the subgroup of five subjects treated with a final dose of 200 mg/day. Fluvoxamine co-administration with risperidone was well tolerated and no patient developed extrapyramidal side effects. These findings indicate that fluvoxamine at dosages up to 100 mg/day is not associated with clinically significant changes in plasma risperidone concentrations. However, higher doses of fluvoxamine may elevate plasma risperidone levels, presumably as a result of a dose-dependent inhibitory effect of fluvoxamine on CYP2D6-and/or CYP3A4-mediated 9-hydroxylation of risperidone.

Keywords: Risperidone; 9-Hydroxyrisperidone; Fluvoxamine; Drug interaction; CYP2D6; CYP3A4

1. Introduction

Risperidone is a second-generation antipsychotic drug with potent antagonistic properties at serotonin 5-HT_{2A} and dopamine D₂ receptors [1]. This agent is effective in the treatment of both positive and negative symptoms and, possibly, other symptom dimensions in schizophrenia and has a lower potential to cause extrapyramidal symptoms compared with conventional antipsychotics [1]. However, like first-generation antipsychotics, risperidone can induce an increase in serum prolactin levels [2].

Risperidone is extensively metabolized in the liver, primarily by 9-hydroxylation, yielding an active metabolite 9-hydroxyrisperidone (9-OH-risperidone) [3]. According to in

vivo and in vitro studies, cytochrome P450 (CYP) enzymes CYP2D6 and, to a lesser extent, CYP3A4 are responsible for the 9-hydroxylation of risperidone [4–7]. As 9-OH-risperidone is approximately equipotent with the parent drug in terms of dopamine receptor affinity, the total risperidone active moiety (risperidone plus 9-OH-risperidone) is regarded to contribute to the overall antipsychotic effect [8]. It is well documented that co-administration of CYP2D6 inhibitors or CYP3A4 inhibitors/inducers may affect total plasma risperidone concentrations with potential clinical implications [9]. In this respect, it has been reported that concomitant treatment with fluoxetine or paroxetine, selective serotonin reuptake inhibitors (SSRIs) with potent inhibitory activity on CYP2D6, may cause a significant elevation in the plasma concentrations of the active fraction of risperidone, possibly associated with occurrence or worsening of extrapyramidal side effects [10–12].

Fluvoxamine is a selective serotonin reuptake inhibitor (SSRI) widely used in the treatment of depression and other psy-

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chiatric disorders [13]. Like other SSRIs, fluvoxamine may be co-administered with antipsychotics in schizophrenic patients with concomitant depressive or negative symptoms [14]. Fluvoxamine interacts with several CYP isoenzymes in vitro: it is a potent inhibitor of CYP1A2 and CYP2C19 and a moderate inhibitor of CYP2C9 and CYP3A4, while it affects only slightly CYP2D6 activity [15–19]. Due to this non-selective inhibition of various CYP isoenzymes, fluvoxamine has a high potential for metabolic drug interactions in vivo [20].

Aim of the present study was to investigate the effect of fluvoxamine on steady-state plasma concentrations of risperidone and 9-OH-risperidone in patients with schizophrenia given fluvoxamine in addition to an ongoing treatment with risperidone.

2. Patients and methods

2.1. Patients

Eleven outpatients (seven men and four women, aged 26–51 years) participated in the study. They had a diagnosis of schizophrenia according to DSM IV and were stabilized on risperidone. The protocol was approved by a local Ethics Committee and written informed consent was obtained from the patients or their relatives.

2.2. Study design

All patients, stabilized on risperidone, at a constant dosage (3–6 mg/day, given as two divided daily administrations) for at least 4 weeks, received adjunctive fluvoxamine to treat residual negative symptoms, concomitant depression or both. Fluvoxamine was administered at a dose of 100 mg/day orally in the evening for 4 consecutive weeks. At the end of week 4, the dose of fluvoxamine could be adjusted by the treating physician on the basis of the individual response and then maintained until the end of week 8. The dosage of risperidone was kept constant throughout the duration of the study, and use of other drugs known to act as inhibitors or inducers of risperidone metabolism was not allowed. Concomitant treatment with other medication, when present, also remained unchanged.

Blood samples for pharmacokinetic evaluations were drawn into heparinized tubes at 8:00 a.m. (12–13 h after the last dose of risperidone and fluvoxamine and immediately before the morning risperidone dose) in the week before starting fluvoxamine (baseline) and after 4 and 8 weeks of fluvoxamine co-administration. The plasma was separated immediately and stored at -20°C until assayed.

Tolerability was assessed by interview and a medical examination at baseline and after 4 and 8 weeks of combination therapy, while extrapyramidal side effects were specifically evaluated at the same times by using the Simpson and Angus Scale (SAS) [21]. Because of the uncontrolled design, the small and heterogeneous sample, the clinical efficacy of the combination was not evaluated.

2.3. Drug assays

Steady-state plasma concentrations of risperidone and 9-OH-risperidone were measured by HPLC according to the method of Avenoso et al. [22]. The limit of quantification of the assay was 2 ng/mL for both analytes. As analytical method allows co-extraction of fluvoxamine, its detection in the chromatogram was used as a measure of compliance.

2.4. Statistical analysis

Plasma concentrations of risperidone, 9-OH-risperidone and their sum (active moiety) before and during fluvoxamine administration were compared by the Student's *t*-test with Bonferroni's correction for multiple comparisons. Changes in plasma risperidone/9-OH-risperidone ratio and in SAS scores before and during fluvoxamine treatment were compared by the Wilcoxon signed-rank test. Results are given in the text as mean \pm S.D. A *P*-value < 0.05 was regarded as statistically significant.

3. Results

Demographic data of the patients participating to the study and individual plasma concentrations of risperidone, 9-OH-risperidone and active moiety before and during fluvoxamine augmentation are reported in Table 1. After 4 weeks of fixed fluvoxamine dose, six patients were maintained on the fluvoxamine dose of 100 mg/day, while the dose was increased to 200 mg/day in the other five subjects. Mean plasma concentrations of risperidone, 9-OH-risperidone and active moiety were not significantly modified during the first 4 weeks of fluvoxamine coadministration (with all patients receiving the dose of 100 mg/day). At week 8, in the six patients stabilized on 100 mg/day, plasma concentrations of risperidone and metabolically derived 9-OH-risperidone did not differ from values at baseline and at week 4, so that levels of the active moiety remained unchanged. In the five patients on a final dose of 200 mg/day, mean plasma concentrations of risperidone increased significantly ($P < 0.05$) from 7 ± 2 ng/mL at baseline to 9 ± 2 ng/mL at week 4, and to 13 ± 4 ng/mL at week 8, whereas levels of 9-OH-risperidone were not significantly affected. As a consequence, mean concentrations of risperidone active moiety increased significantly ($P < 0.05$) from 46 ± 6 ng/mL at baseline to 50 ± 5 ng/mL at week 4, and to 58 ± 11 ng/mL at week 8 of fluvoxamine co-administration. Moreover, in this subgroup of subjects, plasma risperidone/9-OH-risperidone ratios increased significantly ($P < 0.05$) during fluvoxamine cotreatment from 0.16 ± 0.05 at baseline to 0.28 ± 0.05 at final evaluation.

No symptoms ascribed to risperidone toxicity were observed throughout the overall study period. No patient developed extrapyramidal side effects during adjunctive fluvoxamine treatment and SAS scores remained substantially unchanged during adjunctive therapy. Two patients complained of oversedation and one of mild nausea during the first few days of fluvoxamine administration.

Table 1

Demographic data and plasma concentrations of risperidone, 9-OH-risperidone and active moiety before and during fluvoxamine treatment in 11 patients with schizophrenia

Patient no.	Sex	Age (years)	Risperidone dose (mg/day)	Risperidone levels (ng/mL)			9-OH-risperidone levels (ng/mL)			Active moiety levels (ng/mL)		
				Baseline	Week 4	Week 8	Baseline	Week 4	Week 8	Baseline	Week 4	Week 8
1	F	37	4	9	7	11	28	35	40	37	42	51
2	M	45	6	4	6	8	41	32	34	45	38	42
3	M	41	4	3	3	8	34	50	40	37	53	48
4	F	34	3	7	10	8	27	27	36	34	37	44
5	M	51	4	4	6	5	36	23	33	40	29	38
6	F	27	6	8	5	9	52	57	47	60	62	56
7	M	43	4	7	9	13 ^a	41	46	48 ^a	48	55	61 ^a
8	M	49	6	8	11	13 ^a	42	36	40 ^a	50	47	53 ^a
9	M	26	3	4	7	8 ^a	32	36	35 ^a	36	43	43 ^a
10	F	46	6	9	9	18 ^a	39	43	54 ^a	48	52	72 ^a
11	M	35	6	5	7	11 ^a	45	45	48 ^a	50	52	59 ^a
Mean \pm S.D. ^b				4.7 \pm 1.3	6 \pm 2	7 \pm 2	38 \pm 7	39 \pm 10		44 \pm 8	46 \pm 10	

^a Fluvoxamine dose 200 mg/day.

^b Mean values at week 8 were not reported as patients were receiving different fluvoxamine daily doses.

4. Discussion

Augmentation of SSRIs to risperidone is relatively common and proposed for the treatment of depressive and negative symptoms of schizophrenia [14]. Moreover, risperidone may be added to SSRIs to improve response in patients with major depression or obsessive-compulsive disorder [23,24]. However, these combinations may result in clinically relevant pharmacokinetic interactions as a consequence of the differential inhibitory effects of SSRIs on CYP enzymes [25]. In this respect, formal kinetic studies in patients with schizophrenia have reported that paroxetine and fluoxetine increased plasma concentrations of risperidone active moiety by 45 and 75%, respectively, sertraline caused a minimal, dose-dependent elevation of total risperidone concentrations, while citalopram did not modify significantly the plasma levels of risperidone and its metabolite [10,11,26,27]. With regard to other newer antidepressants, reboxetine and mirtazapine do not cause significant modifications of plasma concentrations of risperidone active fraction [28,29].

In the current study, a 4-week addition of fluvoxamine, at doses of 100 mg/day, to pre-existing risperidone therapy was associated with no significant changes in plasma concentrations of risperidone, 9-OH-risperidone and the active moiety. However, while in the six patients stabilized on 100 mg/day plasma levels of risperidone and its metabolite were still unchanged at week 8, in the five patients receiving the highest dose of fluvoxamine, 200 mg/day, plasma concentrations of risperidone were almost doubled at final evaluation as compared to baseline, while levels of the metabolite were substantially unchanged. As a result, a slight, but significant increase (by a mean 26%) in plasma concentration of risperidone active fraction was observed in this subgroup of patients at week 8 as compared to pretreatment values. However, due to the limited number of patients treated with the highest fluvoxamine dose, our findings can be regarded as preliminary and the reported evidence of a dose-dependent effect of fluvoxamine on plasma risperidone concen-

trations needs to be investigated by a complete pharmacokinetic study.

The results of the present investigation are substantially in line with previous findings indicating that fluvoxamine, at its usually effective dose of 100 mg/day, has a low potential for CYP2D6-mediated drug interactions [17–19]. In this respect, in vitro research has demonstrated that fluvoxamine has a weaker inhibitory effect on CYP2D6 activity as compared to other SSRIs such as fluoxetine, norfluoxetine and paroxetine [15,17,19]. Consistent with this, fluvoxamine, 100 mg/day, has been reported to have relatively modest in vivo effects on CYP2D6 substrates such as dextromethorphan [30] and desipramine [31]. To explain the minimal elevation in total plasma risperidone levels and the associated increase in risperidone/9-OH-risperidone ratio in the subgroup of subjects receiving the highest fluvoxamine dose, it can be speculated a dose-dependent inhibitory effect of fluvoxamine on the 9-hydroxylation of risperidone, presumably mediated by inhibition of CYP2D6 and/or CYP3A4. In fact, fluvoxamine is a moderate inhibitor of CYP3A4 [19], which plays a role in the biotransformation of risperidone [6,7]. On the other hand, the observation that in these subjects the levels of 9-OH-metabolite did not decrease as a result of the interaction may be explained by assuming that fluvoxamine also inhibited the further biotransformation of 9-OH-risperidone and/or affected alternative routes of risperidone metabolism, such as *N*-dealkylation or 7-hydroxylation [3].

While fluvoxamine appears to affect minimally and in a dose-dependent manner the elimination of risperidone, it should be pointed out that this agent, already at the dose of 100 mg/day, may cause a significant elevation of plasma concentration of various antipsychotics, such as haloperidol (1.8–4.2-fold increase), clozapine (up to 5–10-fold) and olanzapine (up to 2-fold), due to its potent inhibitory effect on CYP1A2, CYP2C19 and, to a lesser extent, CYP3A4, the major CYP isoforms involved in the biotransformation of these compounds [32–35].

The combination risperidone-fluvoxamine was safe and well tolerated and no patient experienced extrapyramidal symptoms. However, it should be underlined that the concentrations of risperidone active fraction reached at final evaluation by one of the patients on the highest fluvoxamine dose were close to the threshold values (around 70–80 ng/mL) more frequently associated with parkinsonian side effects [36].

In conclusion, our findings indicate that augmentation of risperidone therapy with fluvoxamine at dosages up to 100 mg/day is not associated with clinically significant changes in plasma risperidone concentrations. However, in consideration of a dose-dependent elevation of total risperidone levels, careful clinical observation and monitoring of plasma risperidone levels may be of value in the management of patients receiving higher fluvoxamine doses.

Acknowledgement

Supported by grants from the University of Messina (PRA 2000).

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